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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/513,086	02/24/00	MANSFIELD L	MSU 4.1-458

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HM22/0816

EXAMINER	
CONNELL, Y	
ART UNIT	**PAPER NUMBER**
1633	3

DATE MAILED: 08/16/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/513,086	Mansfield et al
Examiner	Group Art Unit
Yvette Connell Albert	1633

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-50* is/are pending in the application.

Of the above, claim(s) *1-3, 10-12, 18-22, 29-44, 47 and 48* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *4-9, 13-17, 23-28, 45, 46, 49, and 50* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 2

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-3, 21-22, drawn to a vaccine comprising antibodies, classified in class 424, subclasses 130.1 and 184.1 .

II. Claims 4-9, 13-17, 23-28, 45-46, 49-50, drawn to vaccine comprising antigens, and method of protecting equids via said vaccine, methods of producing polypeptides, classified in class 424, subclass 184.1, class 514, subclass 44, and class 435, subclass 69.1

III. Claims 10-12, 18-20, 44-45, 47-50, drawn to vaccine of DNA encoding an antigen, and method of protecting equid against infection via said vaccine, classified in class 424, subclass 185.1 and class 514, subclass 44.

IV. Claims 29-35, drawn to methods for producing antibodies, classified in class 435, subclass 70.1.

V. Claim 36 , drawn to a monoclonal antibody which selectively binds to antigen, classified in class 530, subclass 387.1.

VI. Claim 37, drawn to an isolated recombinant protein, classified in class 530, subclass 350.

2. The inventions are distinct, each from the other because of the following reasons: Inventions I-III are related in that they are all vaccines utilized in protection against infection. However, the inventions are distinct each from the other as the vaccine of invention I, comprises antibodies, the vaccine of invention II comprises antigens, while the vaccine of invention III comprises DNA encoding an antigen. Additionally, polynucleotides, polypeptides, and antibodies can be used by materially different methods. For example, polynucleotides can be used as hybridization probes for screening cDNA and genomic libraries, polypeptides can be used for antigen presenting cell priming, and antibodies can be used in screening assays. The differences between the inventions are further underscored by their divergent classification and independent search status.

Invention II is related to invention VI as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case, the product of invention VI can be made by another materially different process such as enzymatically or isolated from cells endogenously producing the protein. The differences between the inventions are further underscored by their divergent classification and independent search status.

Inventions IV and V are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be

used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case, the product of invention V can be made by another materially different process by isolating from cells endogenously producing the antigen and then using the antigen to make the antibody. The differences between the inventions are further underscored by their divergent classification and independent search status.

Inventions I-III are distinct from inventions IV-VI since it can be shown that they have different modes of operation, different functions and different effects. The polypeptides are distinct in chemical structure, function as well as therapeutic function from the antibodies, as well as the vaccines which elicit an immune response and provide protection against infection. Furthermore, the inventions of groups II-III involve modifying cellular effects in vivo, requiring different technical considerations and different reagents not involved in the methods and products of the other inventions. The differences between the inventions are further underscored by their divergent classification and independent search status.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their recognized divergent subject matter, and further because the searches required for the different inventions are not coextensive, restriction for examination purposes as indicated is proper.

During a telephone conversation with Ian McCleod on 7/13/00, and again on 7/27/00 a provisional election was made **without** traverse to prosecute the invention of Groups II

claims 4-9, 13-17, 45-46, 49-50, and Group IV, claims 23-28. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-3, 10-12, 18-22, 29-44, and 47-48, are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(h).

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 4-9, 13-17, 45-46, and 49-50, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

1. Claimed invention. The claims are drawn to a vaccine for active immunization of an equid against a *Sarcocystis neurona* infection comprising at least one epitope of a unique 16+/-4 or

30+/-4 antigen of said parasite; wherein the antigen is a polypeptide produced in a plasmid in E. coli; wherein the antigen is a fusion polypeptide consisting of glutathione S-transferase, protein A, maltose binding protein, and polyhistidine; and provided in a pharmaceutically acceptable carrier. The claims are also drawn to a method for vaccinating an equid against infection via said vaccine and wherein the DNA in the plasmid is operably linked to a promoter which enables transcription; a method of protecting an equid against infection via said vaccine, administered by a vaccination route selected from the group consisting of intranasal, intramuscular administration and intraperitoneal, intradermal, and subcutaneous injection. The claims are further drawn to a method for producing a polypeptide, comprising: providing a microorganism in a culture containing a DNA encoding a fusion polypeptide comprising at least one epitope of a 16 +/-4kDa and/or 30 +/-4kDa antigen of S. neurona, and a polypeptide that facilitates isolation of the fusion polyypeptide, culturing the microorganism in culture to produce the fusion polypeptide, and isolating the fusion polypeptide.

2. The *in vitro* examples and results on pages 33-44 shows that applicant was successful in preparing monoclonal antibodies which recognize 16+/-4 kDa antigen and/ or 30+/-4 kDa antigen of *Sarcocystis neurona*. Applicant was also successful in preparing a cDNA library which expresses said antigens of *Sarcocystis neurona*; isolating, excystation and culturing *Sarcocystis* species using opossums as a model, and finally, applicant was successful in providing chemical excystation methods for preparing *Sarcocystis* sp. oocysts.

3. It is not readily apparent that one skilled in the art given applicant's disclosure, would be able to practice the invention over the scope as claimed in view of the lack of guidance provided in the specification as filed.

The specification is not enabling in its disclosure as it fails to teach whether the vaccine for active immunization would in fact induce a protective effect *in vivo*, especially in an equid. Furthermore, the vaccines of the instant invention implies protection of an equid against *S. neurona* infection. The specification does not indicate or demonstrate any *in vivo* results obtained by actively immunizing any host, such that hosts if and when challenged, said hosts would be protected from developing an infection due to *S. neurona*. In addition, the specification fails to teach the correlation between the *in vitro* results shown and *in vivo* protection of any hosts against *S. neurona* infection, by the vaccine composition of the present invention. Therefore, the specification appears to be wholly prophetic in its vaccine composition and methods of conferring protection via said vaccine to equids, against *S. neurona* infection.

4. The physiological art of utilizing a vaccine for active immunization of equids against Sarcocystis neurona infection at the time of the invention would have been considered unpredictable. According to Kisthardt et al, 1997, vaccination of horses against S. neurona infection would aid in the prevention of EPM or equine protozoal myeloencephalitis, but currently, no vaccines are available. Once the horse/opossum life cycle is confirmed and reproduced experimentally then the development of effective vaccines should follow(Kisthardt, see page 13 1st para).

Furthermore, Liang et al, 1998, states that although no successful vaccine against related apicomplexan parasites has been widely used, there are encouraging signs that such a vaccine is possible(Liang, see page 1834, left col, 2nd para). In addition, CSF or cerebrospinal fluid samples with different immunoblot band patterns strongly suggest that antibodies specific for Sn 14 and Sn 16 have protective activity against S. neurona, at least in vitro, while antibodies to Sn 30 are not recognized as specific since a 30 kDa antigen immunoreactive with sera from horses with EPM is found in other Sarcocystis spp(Liang, see page 1837, left col, 1st para). . . S. neurona infection of the horse induces production of antibodies to Sn 14 and Sn 16, indicating that these two proteins are expressed in vivo and are strong immunogens in the horse, and as such they warrant further investigation as candidate antigens for inclusion in vaccines against S. neurona infection(Liang, see page 1837, right col, last para).

5. In the absence of specific guidance which is lacking in the specification as filed and given the state of the art at the time of filing, coupled with the reasons discussed above, it would require undue experimentation for one skilled in the art to practice the methods or use the claimed products as disclosed in the specification.

The quantity of experimentation required to practice the invention as claimed would require the identification of the specific surface antigens, Sn 16 and Sn 30, from a parasite [S. neurona] which may express different proteins at different stages of *in vivo* or *in vitro* development, some proteins may be expressed and function essentially only *in vitro*, and such proteins would be inappropriate targets for vaccine development(Liang et al, see page 1837, last

para). Therefore, it would require undue experimentation to identify and isolate specific surface antigens which would be effective both *in vitro* and *in vivo*, especially in the absence of an in vivo model, in protecting against *S. neurona* infection. This is considered trial and error experimentation and as such is considered undue.

5. Claims 23-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a polypeptide comprising providing Sarcocystis neurona in a culture containing a DNA encoding a fusion polypeptide comprising at least one epitope of a 16 +/- 4 and /or 30 +/- 4 kDa antigens of *Sarcocystis neurona* and a polypeptide that facilitates isolation of the fusion polypeptide; culturing the microorganism in a culture to produce the fusion polypeptide and isolating the fusion polypeptide, does not reasonably provide enablement for any method of producing any polypeptide comprising providing any microorganism containing any DNA encoding any fusion polypeptide comprising at least one epitope of a 16 +/- 4 and /or 30 +/- 4 kDa antigens of *Sarcocystis neurona* and any polypeptide that facilitates isolation of the fusion polypeptide; culturing the microorganism in any culture to produce the fusion polypeptide and isolating the fusion polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

1. Claimed invention. The claims are drawn to a method for producing a polypeptide by providing a microorganism containing a DNA encoding a fusion polypeptide comprising at least

one epitope of a 16 +/- 4 and /or 30 +/- 4 kDa antigens of *Sarcocystis neurona* and a polypeptide that facilitates isolation of the fusion polypeptide; culturing the microorganism in any culture to produce the fusion polypeptide and isolating the fusion polypeptide. The claims are also drawn to said method for producing a polypeptide wherein isolating the fusion polypeptide is by affinity chromatography; and wherein the polypeptide is all or a portion of protein A and the affinity chromatography comprises an IgG-linked resin; wherein the polypeptide is polyhistidine and the affinity chromatography comprises a Ni2+ resin; wherein the polypeptide is glutathione S-transferase and the affinity chromatography comprises a glutathione Sepharose 4B resin; and wherein the polypeptide is maltose binding protein and the affinity chromatography comprises an amylose resin.

2. The *in vitro* examples and results on pages 33-44 shows that applicant was successful in preparing monoclonal antibodies which recognize 16+/-4 kDa antigen and/ or 30+/-4 kDa antigen of *Sarcocystis neurona*. Applicant was also successful in preparing a cDNA library which expresses said antigens of *Sarcocystis neurona*; isolating, excystation and culturing *Sarcocystis* species using opossums as a model, and finally, applicant was successful in providing chemical excystation methods for preparing *Sarcocystis* sp. oocysts.

3. It is not readily apparent that one skilled in the art given applicant's disclosure, would be able to practice the invention over the scope as claimed in view of the lack of guidance provided in the specification as filed.

The specification is not enabling in its disclosure as it fails to teach a specific or preferred expression system, whether bacterial or eukaryotic expression system, for producing the antigens of the present invention.

4. The physiological art of producing polypeptides by providing microorganisms in culture containing DNA encoding a fusion polypeptide and polypeptide which facilitates isolation of the fusion polypeptide, culturing the microorganism in a culture to produce the fusion polypeptide and isolating the fusion polypeptide, at the time of the invention was well established and yielded excellent results by those skilled in the art.

5. In the absence of specific guidance which is lacking in the specification as filed, and given the state of the art at the time of filing, coupled with the reasons discussed above, it would require undue experimentation for one skilled in the art to practice the methods or use the claimed products as disclosed in the specification.

The quantity of experimentation required to practice the invention as claimed would require one to select a microorganism in a specified culture medium, containing DNA encoding a fusion polypeptide comprising an antigen of S. neurona, and a polypeptide which facilitates isolation of the fusion polypeptide; culturing the microorganism in a culture to produce the fusion polypeptide and isolating the fusion polypeptide. This is trial and error experimentation as one must select any microorganism from any source or origin, bacterial or eukaryotic, which contains a DNA encoding a fusion polypeptide which comprises at least one epitope of said Sn antigen, which when combined with another polypeptide would facilitate the isolation of the fusion

polypeptide. There are innumerable permutations associated with this experiment as one must decide which specific microorganism with which DNA encoding fusion polypeptide, and in the present of which other polypeptide would result in the desired product. In the absence of specific guidance, this is considered an invitation to experimentation and as such is considered undue.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 4 is rejected under 35 U.S.C. 102(b) as being anticipated by Liang et al, 1998.

Applicant's claims are essentially directed to a composition comprising at least one epitope of a unique 16 +/- 4 antigen of *Sarcocystis neurona*.

Liang et al teaches that *S. neurona* surface proteins Sn 14 and Sn 16 kDa, were isolated by a combination of surface protein labeling, immunoprecipitation and Western blotting(see page 1836, left col, 1st para), which could be useful as components of a vaccine against S. neurona infection(see abstract).

Therefore, the claimed invention was anticipated by Liang et al who taught at least one epitope of a unique 16 +/- 4 antigen of *Sarcocystis neurona* in isolation, and which could be used in vaccine compositions.

Claims 5-9, 13-17, 23-28, 45-46, and 49-50 are free of the prior art. However, the closest related prior art to Liang et al, 1998, teaches *S. neurona* surface proteins Sn 14 and Sn 16 may be useful components of a vaccine against *S. neurona* infection, but does not teach surface protein Sn 30, or a method for producing a polypeptide, comprising: providing a microorganism in a culture containing a DNA encoding a fusion polypeptide comprising at least one epitope of a 16 +/-4kDa and/or 30 +/-4kDa antigen of S. neurona, and a polypeptide that facilitates isolation of the fusion polyypeptide, culturing the microorganism in culture to produce the fusion polypeptide, and isolating the fusion polypeptide, as broadly claimed.

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yvette Connell, whose telephone number is 703-308-7942. The examiner can normally be reached on Monday-Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 703-308-0447.

Any inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Yvette Connell

July 31, 2000

JOHN L. LeGUYADER
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